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By

Evelyn Sabatino
(Signature of person mailing)

Evelyn Sabatino
(Typed or printed name of person)



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: John A. Lowe

Examiner: Cybille Delacroix-Muirheid

APPLICATION NO.: 09/007,268

Group Art Unit: 1654

FILING DATE: January 14, 1998

TITLE: Fluoroalkoxybenzylamino Derivatives
of Nitrogen Containing Heterocycles

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Communication and Amendment

In connection with Applicant's review of the pending Official Action, it was determined that the Patent Office copy of the Specification herein may be missing Page 41. The missing text is identical to text of PCT/US92/03571 which, at entry into the U.S. national stage, became Serial No. 08/167,881. The present application is a divisional of the '881 application. Since there has been a continuous chain of co-pendency, entry of the text, if determined to be missing, is appropriate.

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Amendment

Please insert the attached page (numbered as page 41), into the Specification as page 41.

Respectfully submitted,

Date: 12/20/99

E. Victor Donahue
E. Victor Donahue
Attorney for Applicant(s)
Reg. No. 35,492

Pfizer Inc
Patent Department, 20th Floor
235 East 42nd Street
New York, NY 10017-5755
(212) 733-2739

and washed with ether to obtain 600 mg of the title compound, m.p. > 250°C.

¹H NMR (free base, CDCl₃) δ 1.36 (s, 1H), 1.54 (m, 1H), 1.86 (m, 1H), 2.06 (m, 1H), 2.76 (m, 2H), 3.22 (m, 1H), 3.32 (d, 1H, J=15), 3.48 (s, 3H), 3.58 (d, 1H, J=15), 3.85 (d, 1H, J=3), 6.57 (d, 1H, J=9), 6.80 (d, 1H, J=3), 6.92 (dd, 1H, J=3, 9), 7.22 (m, 5H).

HRMS Calc'd for C₂₀H₂₃F₃N₂O₂: 380.1711. Found: 380.1704.

Anal. Calc'd for C₂₀H₂₃F₃N₂O₂•2HCl•0.2H₂O: C 52.57, H 5.60, N 6.13. Found: C 52.58, H 5.40, N 5.97.

EXAMPLE 5

(2S,3S)-1-(5,6-Dimethoxyhexyl)-3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine hydrochloride

Under a nitrogen atmosphere in a round-bottom flask were placed 250 mg (0.66 mmol) of (2S, 3S)-3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine, 2 mL of tetrahydrofuran (THF) and 0.28 mL (2.0 mmol) of triethylamine. To the system were added 475 mg (2.0 mmol) of 5,6-dimethoxy-1-methylsulfonyloxyhexane (prepared from 1,5,6-hexanetriol by sequential acetonide formation (acetone, p-toluenesulfonic acid), acetylation (acetyl chloride, triethylamine, THF), acetonide cleavage (60% acetic acid/water), dimethylation (sodium hydride, methyl iodide, THF), deacetylation (sodium methoxide, methanol) and methanesulfonate ester formation (methanesulfonyl chloride, triethylamine, THF)), and the mixture was heated at 50-60°C for four days. The reaction mixture was partitioned between CHCl₃ and saturated aqueous sodium bicarbonate and extracted with three portions of CHCl₃. The combined organic fractions were dried (Na₂SO₄), filtered and concentrated to obtain 853 mg of an orange oil. The crude material was purified by flash column chromatography (35 g of silica gel) using 1:19 methanol/chloroform as the eluant to obtain 185 mg of yellow oil. The oil was dissolved in ethyl acetate and ether saturated with HCl was added to the solution. The mixture